Risk Assessment Through the Product Life Cycle:
How Can We Do Better?

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The information presented is intended for **general educational purposes only**, and **not as advice for managing specific circumstances**. The opinions expressed, and the methodologies described, are based on the speaker's knowledge and experience, and do not necessarily reflect the views of GlaxoSmithKline.

Current Situation:
We can't predict or identify all safety issues as early as we'd like to.

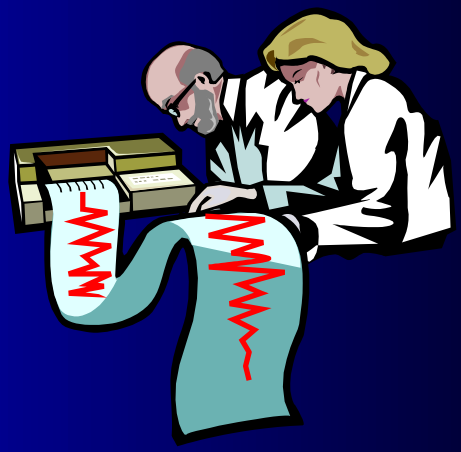
Goal:
To more effectively harness all of the knowledge
that is generated during the drug development process.

Ultimate Benefits:
Safer drugs to the market sooner
Fewer critical safety issues emerging
late in the development process or
after market introduction

Fewer chutes, more ladders!

Two key areas of opportunity

How we work together



How we look at safety data

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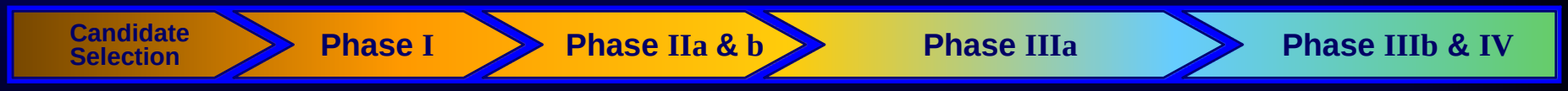
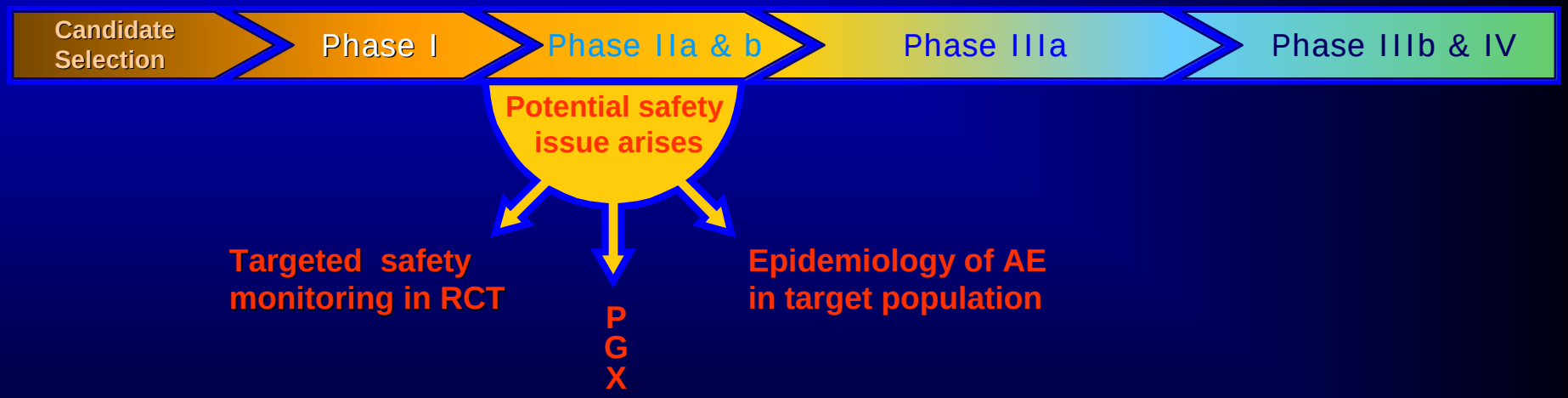
Multi-disciplinary teams have an edge over individual disciplines at detecting and managing risk

- Multi-disciplinary expert teams routinely monitor all aspects of safety
  - Focus on review of integrated data
- Information is captured through a formal benefit-risk management plan:
  - Serves as an ongoing repository for all issues from pre-clinical development through early post-marketing period
  - Enhances retention of institutional knowledge as programs evolve and 'hand-offs' occur



Multi-Disciplinary Safety Review Teams

- **Operating Principles**
  - Review integrated data with state-of-the-art-tools
  - Meet regularly
  - Document decisions & actions
  - Predefine thresholds for key parameters
  - Investigate and follow-up on signals



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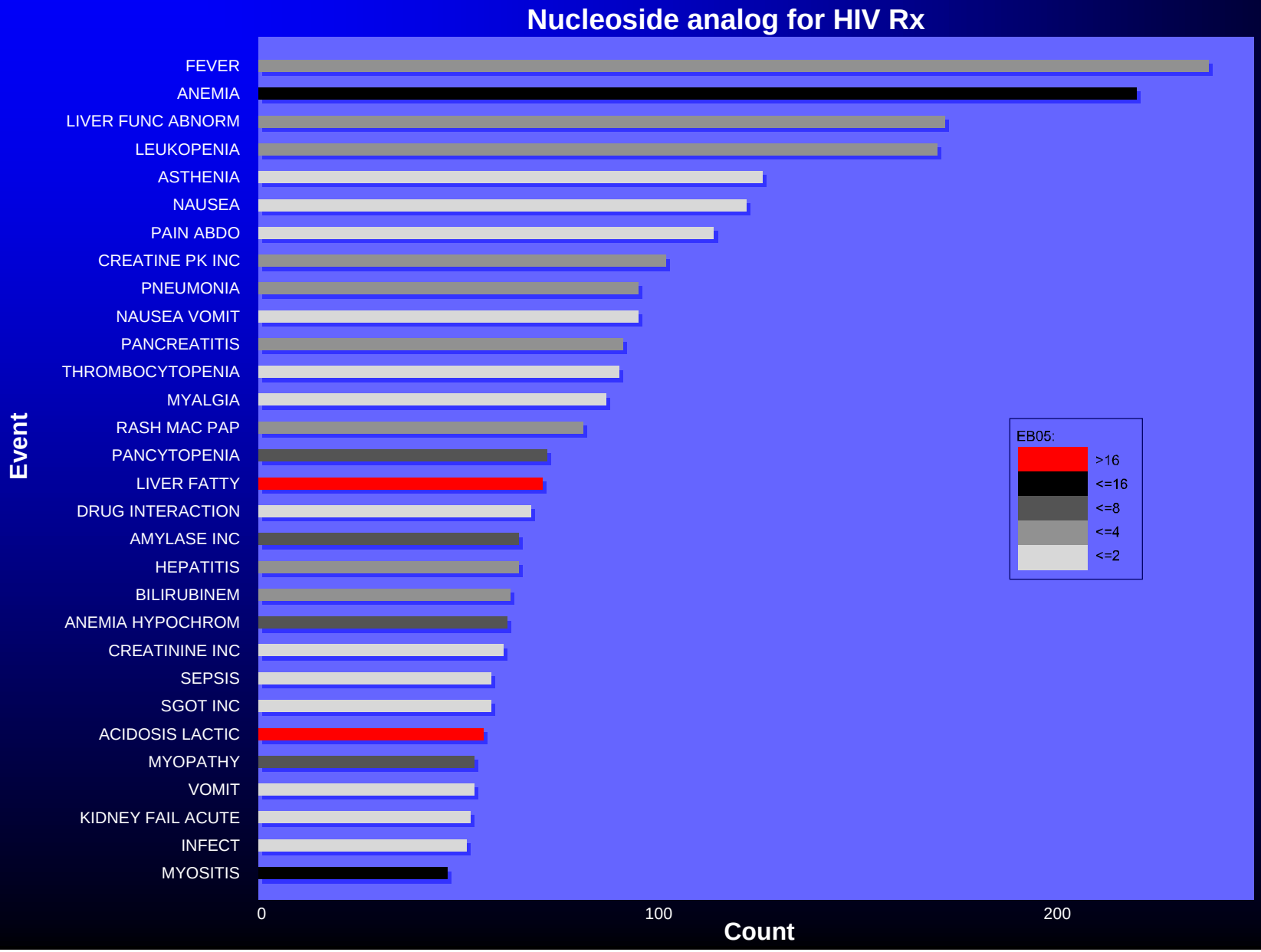
Utilize data mining to examine the safety profile of related molecules to enhance risk management planning



Challenges inherent to the evaluation of clinical safety data

- Clinical development is process ‘highly evolved’ to study efficacy using well defined, uniform endpoints.
- In contrast, not all safety data can be collected in pre-defined endpoints.
  - Although laboratory data is collected in a uniform fashion, adverse events are collected only when they observed through clinical monitoring
  - Studies don’t have adequate power to evaluate all adverse events, particularly rare events (~beta error)
- Additional challenges with safety data include
  - Coding challenges (lumping and splitting)
  - Time dependence of AEs
  - Multiplicity of AEs

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Working with Clinical Safety Data

- Traditional safety analyses focuses on aggregate data.
  - However, outlier data may sometimes reveal safety issues that impact on the benefit-risk profile of the product.
- Therefore, EXPLORATORY ANALYSIS is an invaluable part of safety and risk assessment.
  - We need graphical and visual tools that
    - enable medical reviewers to synthesize large amounts of data
    - permit an interactive approach to examining specific serious safety concerns as they are identified
  - Use of standardized tools by industry and FDA will facilitate both signal detection and communication

From CIOMS VI

(Council for International Organizations of Medical Sciences)

The purpose of statistical analysis in this context is to present the data in a way that facilitates understanding of the effects of a drug. The analysis should make clear whether variation in results is likely to be due to chance or whether substantial effects might still be associated with a drug. It is necessary to be clear when the data are insufficient to draw conclusions on safety. “Absence of evidence is not evidence of absence”.

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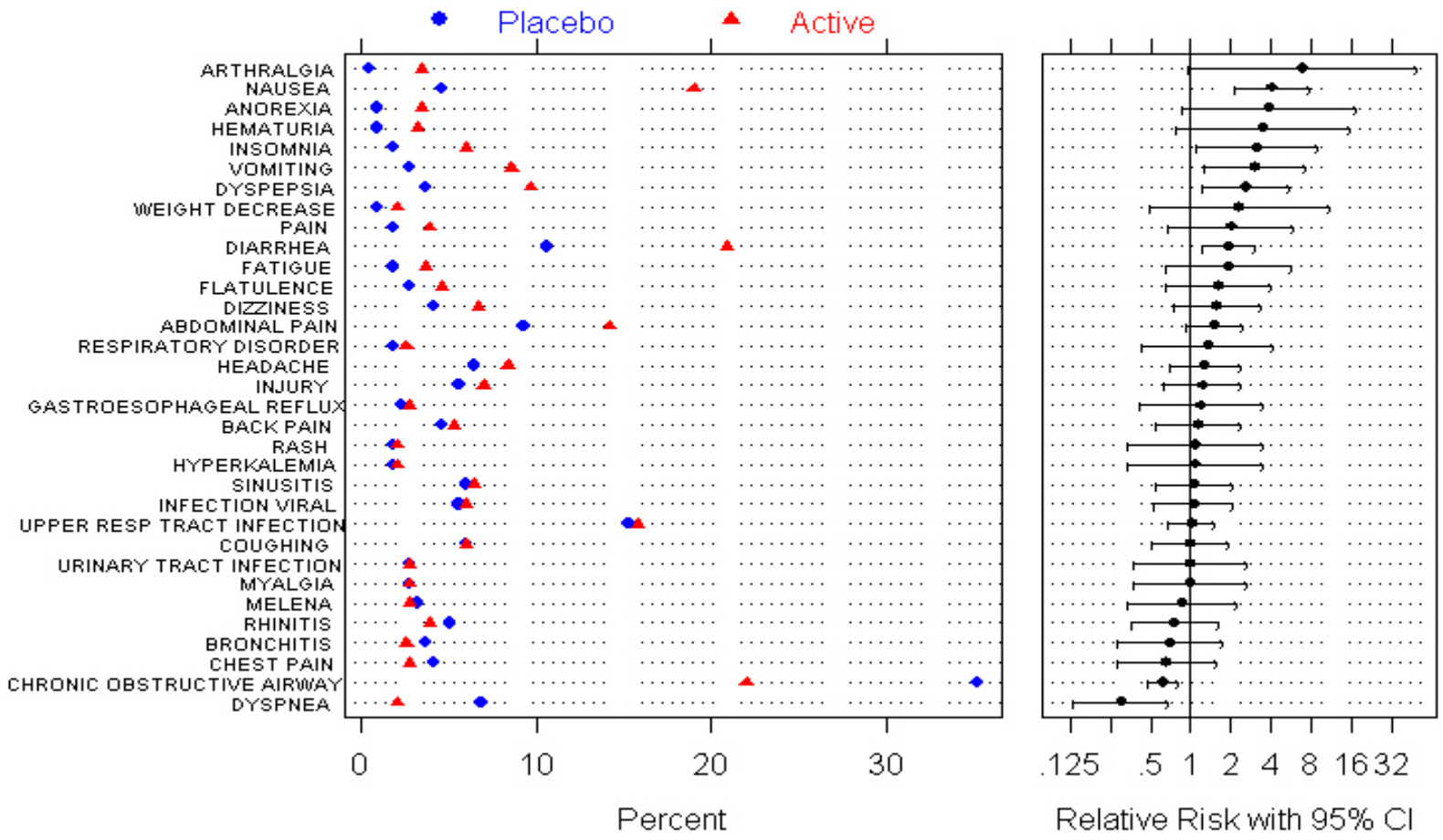
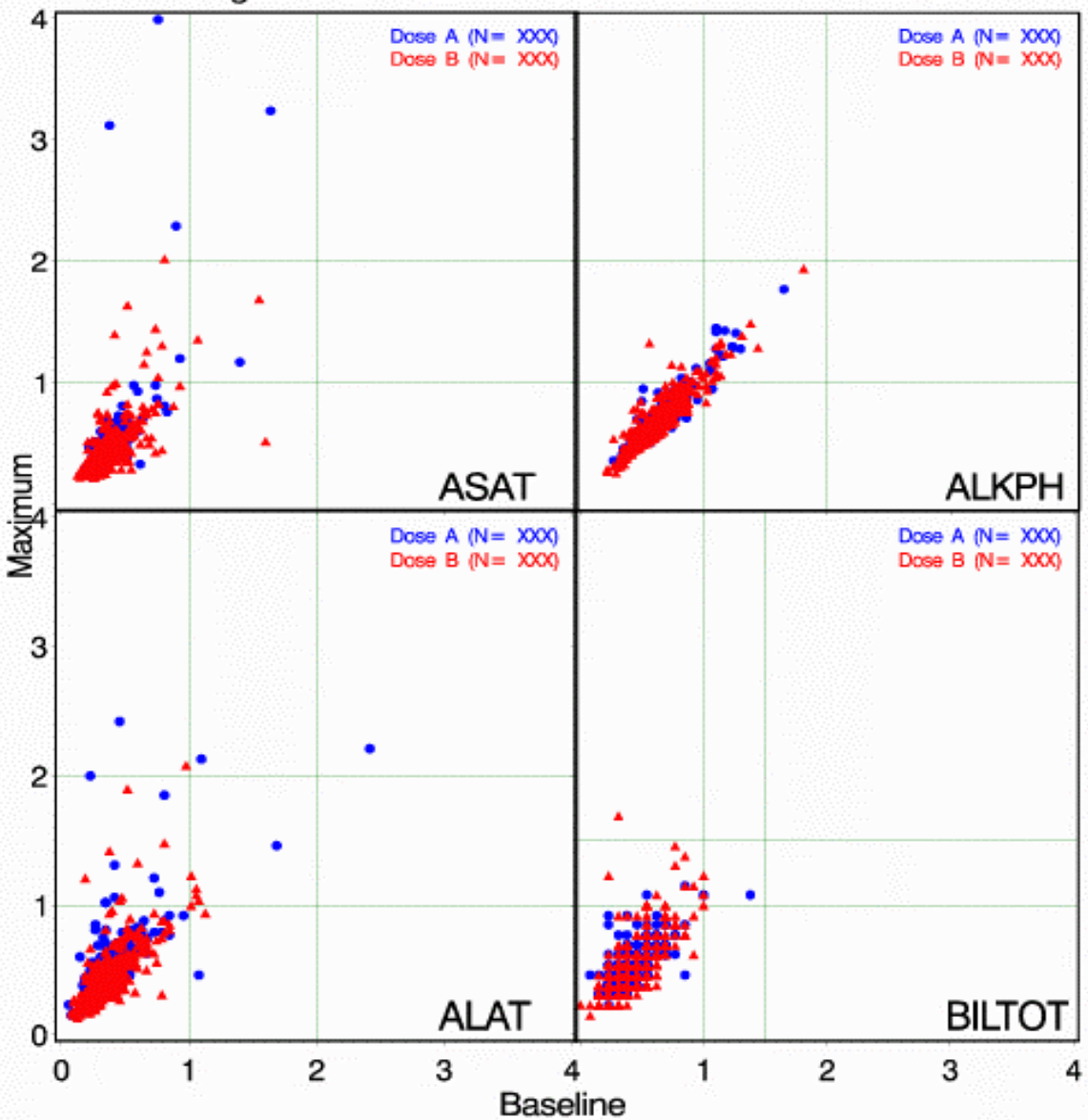
Most Frequent On-Therapy Adverse Events Sorted by Relative Risk



Protocol: Study XZY999
Population: Intent – to – Treat

Figure 5 LFT Scatter Plots of Baseline vs. Maximum



For ASAT, ALAT, and ALKPH, the Clinical Concern level: 2 x ULN, for BILTOT: 1.5 x ULN

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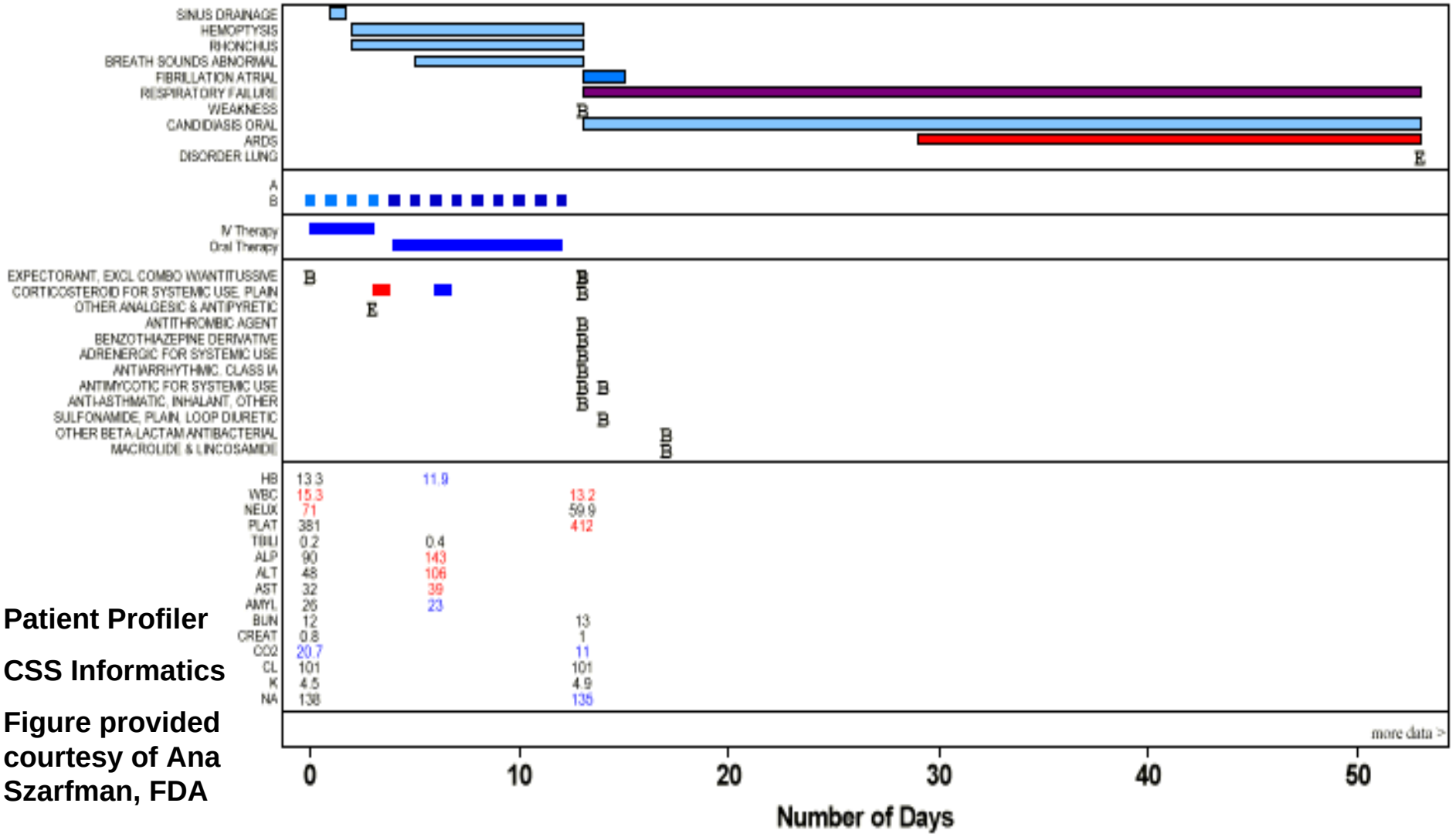
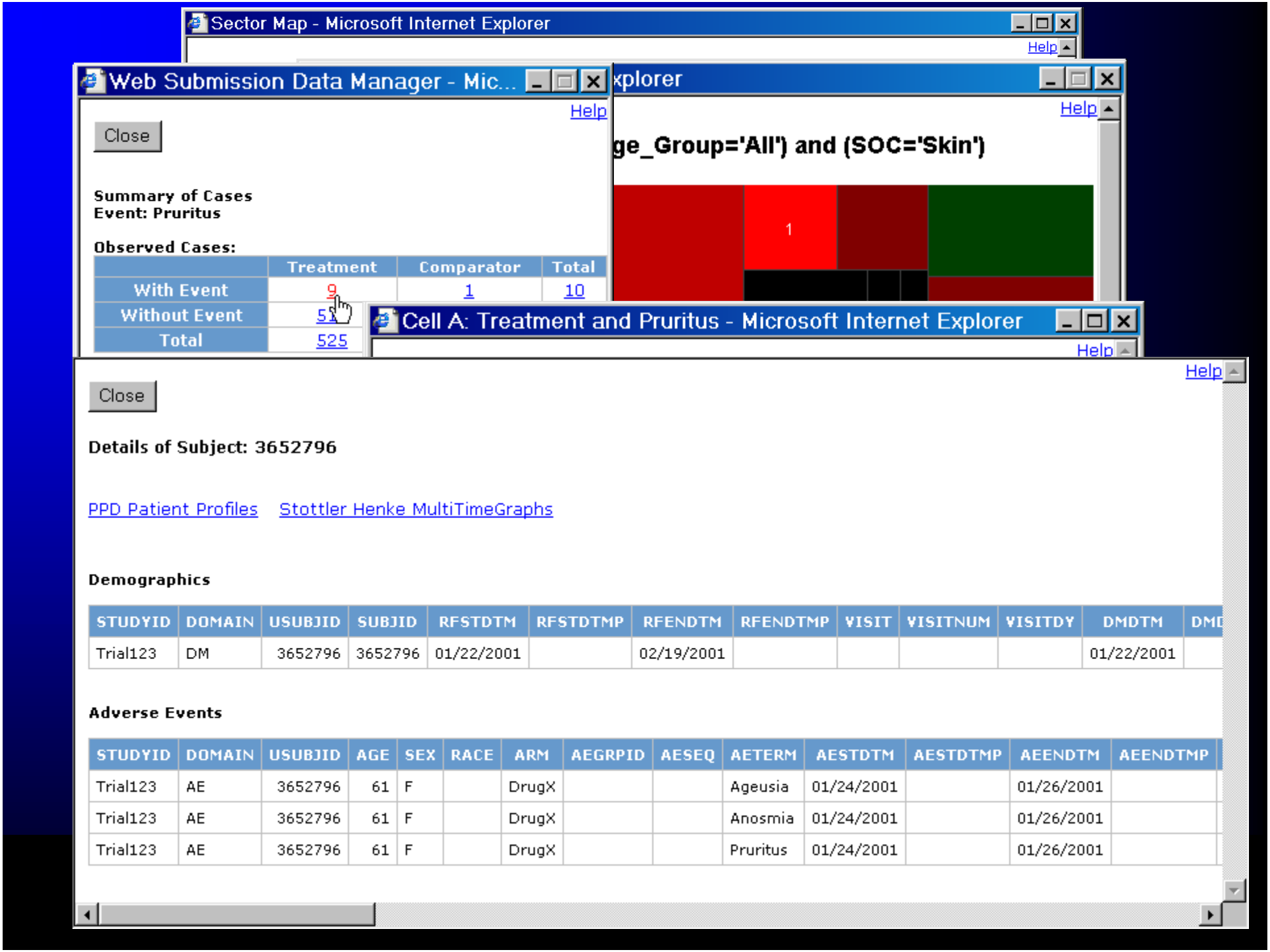
Patient time-line summary graph for Clinical Trial data
AEs, medications, lab results linked on a common timeline



Patient Profiler

CSS Informatics

Figure provided courtesy of Ana Szarfman, FDA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Summary: Quick Wins and Future Directions

Quick Wins for the Critical Path

- Integrated development processes with multi-disciplinary expert teams to address safety issues proactively
- Interactive graphical analytic tools and visualization systems; consider standardization across industry and regulatory agencies
- Deployment of data mining (using human safety or toxicology data) as a means to identify potential safety issues early in development

Future Directions

- Methodology to pick up early safety alarms that predict product ‘demise’
- Better tools to rule out “false safety alarms” that may lead to attrition of potentially viable molecules
- Integrating data from multiple scientific disciplines to optimize the candidate selection process